

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

LISTING OF CLAIMS:

1-10. (Cancelled)

11. (currently amended): A method for treating cartilage-related disease, which ~~comprises-consists of~~ administering a composition ~~consisting essentially of a substance having an EP2 agonist activity~~ to a subject in need of stimulating chondrocyte growth, said composition consisting of a substance having an EP2 agonist activity as an active ingredient for treating cartilage-related disease and a pharmaceutically acceptable carrier.

12-19. (Cancelled)

20. (Previously presented) The method according to claim 11, wherein the cartilage-related disease is cartilage disorder.

21. (Previously presented): The method according to claim 11, wherein the substance having an EP2 agonist activity has one or more effects selected from stimulating chondrogenesis, stimulating chondrocyte growth, stimulating chondrocyte differentiation, inhibiting cartilage calcification and inhibiting cartilage degradation.

22. (Previously presented): The method according to claim 11, wherein the substance having an EP2 agonist activity has one or more effects selected from stimulating integrin mRNA expression, stimulating fibronectin mRNA expression, stimulating cyclin D1 mRNA expression and inhibiting osteopontin mRNA expression.

23. (Previously presented) The method according to claim 21, wherein the one or more effects selected from stimulating chondrogenesis, stimulating chondrocyte growth, stimulating chondrocyte differentiation, inhibiting cartilage calcification and inhibiting cartilage degradation is/are based on one or more effects selected from stimulating integrin mRNA expression, stimulating fibronectin mRNA expression, stimulating cyclin D1 mRNA expression and inhibiting osteopontin mRNA expression on a chondrocyte or a cartilage tissue.

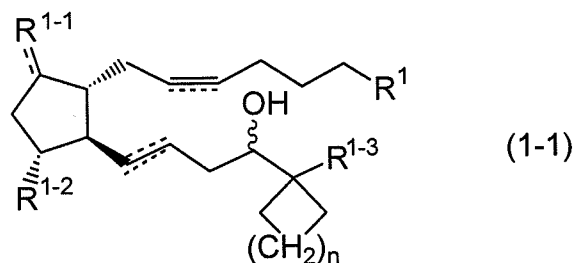
24. (Previously presented) The method according to claim 23, wherein the effect of stimulating chondrocyte growth is based on stimulating cyclin D1 mRNA expression.

25. (Previously presented) The method according to claim 23, wherein the effect of inhibiting cartilage calcification is based on inhibiting osteopontin mRNA expression.

26. (currently amended): A method for treating cartilage-related disease, which ~~comprises~~ consists of administering a composition ~~consisting essentially of (a) a substance having EP2 agonist activity and (b) one or more substances selected from transforming growth factor- β , insulin-like growth factor, basic fibroblast growth factor, epidermal growth factor, growth hormone and platelet-derived growth factor,~~ to a subject in need of stimulating

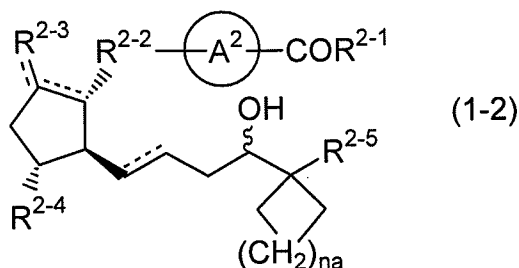
chondrocyte growth, said composition consisting of (a) a substance having EP2 agonist activity and (b) one or more substances selected from transforming growth factor- β , insulin-like growth factor, basic fibroblast growth factor, epidermal growth factor, growth hormone and platelet-derived growth factor, as active ingredients for treating cartilage-related disease, and a pharmaceutically acceptable carrier.

27. (Previously presented) The method according to claim 11, wherein the substance having an EP2 agonist activity is one or more compounds selected from a compound represented by formula (1-1)



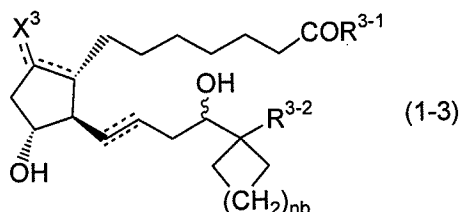
wherein R¹ is carboxy or hydroxymethyl, R¹⁻¹ is oxo, methylene or halogen atom, R¹⁻² is hydrogen atom, hydroxy or C1-4 alkoxy, R¹⁻³ is hydrogen atom, C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, or C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted by 1-3 substituents selected from the following (1) to (5): (1) halogen atom, (2) C1-4 alkoxy, (3) C3-7 cycloalkyl, (4) phenyl or (5) phenyl substituted by 1-3 substituents selected from halogen atom, C1-4 alkyl, C1-4 alkoxy, nitro or trifluoromethyl; n is 0 or 1-4; with the proviso that (1) when 5-6 position is a triple bond, 13-14 position is not a triple bond, (2) when 13-14 position is double bond, the double bond represents E form, Z form or mixture of EZ form or a salt thereof,

a compound represented by formula (1-2)



wherein A^2 is benzene, thiophene or furan ring, R^{2-1} is hydroxy, C1-6 alkoxy or $NR^{2-10}R^{2-11}$ group (wherein R^{2-10} and R^{2-11} are independently hydrogen atom and C1-4 alkyl.), R^{2-2} is C1-4 alkylene, C2-4 alkenylene, -S-C1-4 alkylene, -S-C2-4 alkenylene or C1-4 alkylene-S-, R^{2-3} is oxo, methylene, halogen atom or $R^{2-32}-COO-$ group (wherein R^{2-32} is C1-4 alkyl, C1-4 alkoxy, phenyl, phenyl-C1-4 alkyl, $R^{2-33}-OOC-C1-4$ alkyl or $R^{2-33}-OOC-C2-4$ alkenyl (R^{2-33} is hydrogen atom or C1-4 alkyl).), R^{2-4} is hydrogen atom, hydroxy or C1-4 alkoxy, R^{2-5} is C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted by 1-3 substituents selected from the following (1) to (5); (1) halogen atom, (2) C1-4 alkoxy, (3) C3-7 cycloalkyl, (4) phenyl or (5) phenyl substituted by 1-3 substituents selected from halogen atom, C1-4 alkyl, C1-4 alkoxy, nitro or trifluoromethyl, n_a is 0 or an integer of 1-4, $---$ is a single bond or double bond; with the proviso that, when 8-9 position is double bond, R^{2-3} is $R^{2-32}-COO-$ (wherein R^{2-32} has the same meaning as described above.), R^{2-1} is C1-6 alkoxy or a salt thereof,

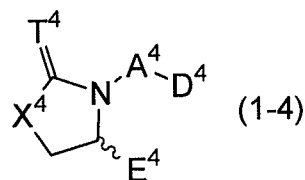
a compound represented by formula (1-3)



wherein R^{3-1} is hydroxy, C1-6 alkoxy or $NR^{3-11}R^{3-12}$ group (wherein R^{3-11} and R^{3-12} are independently, hydrogen atom or C1-6 alkyl.), X^3 is chlorine atom or fluorine atom, R^{3-2} is

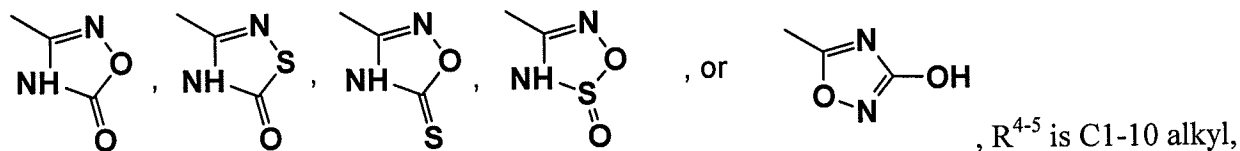
hydrogen atom, C1-8 alkyl, C2-8 alkenyl, C2-8 alkynyl, C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted by 1-3 substituents selected from the following (1) - (5); (1) halogen atom, (2) C1-4 alkoxy, (3) C3-7 cycloalkyl, (4) phenyl or (5) phenyl substituted by 1-3 substituents selected from halogen atom, C1-4 alkyl, C1-4 alkoxy, nitro or trifluoromethyl, nb is 0 or an integer of 1-4 or a salt thereof,

a compound represented by formula (1-4)




wherein T^4 is oxygen atom or sulfur atom, X^4 is $-CH_2-$, $-O-$ or $-S-$, A^4 is A^{4-1} or A^{4-2} , A^{4-1} is C2-8 straight-chain alkylene optionally substituted by 1 to 2 C1-4 alkyl, C2-8 straight-chain alkenylene optionally substituted by 1 to 2 C1-4 alkyl or (3) C2-8 straight-chain alkynylene optionally substituted by 1 to 2 C1-4 alkyl, A^{4-2} is $-G^{4-1}-G^{4-2}-G^{4-3}-$, G^{4-1} is C1-4 straight-chain alkylene optionally substituted by 1 to 2 C1-4 alkyl, C2-4 straight-chain alkenylene optionally substituted by 1 to 2 C1-4 alkyl or C2-4 straight-chain alkynylene optionally substituted by 1 to 2 C1-4 alkyl, G^{4-2} is $-Y^4-$, -ring 1-, $-Y^4$ -ring 1-, -ring 1- Y^4 - or $-Y^4$ -C1-4 alkylene-ring 1-, Y^4 is $-S-$, $-SO-$, $-SO_2-$, $-O-$ or $-NR^{4-1}-$, R^{4-1} is hydrogen atom, C1-10 alkyl or C2-10 acyl, G^{4-3} is a bond, C1-4 straight-chain alkylene optionally substituted by 1 to 2 C1-4 alkyl, C2-4 straight-chain alkenylene optionally substituted by 1 to 2 C1-4 alkyl or C2-4 straight-chain alkynylene optionally substituted by 1 to 2 C1-4 alkyl, D^4 is D^{4-1} or D^{4-2} , D^{4-1} is $-COOH$, $-COOR^{4-2}$, tetrazol-5-yl or $-CONR^{4-3}SO_2R^{4-4}$, R^{4-2} is C1-10 alkyl, phenyl, C1-10 alkyl substituted by phenyl or biphenyl, R^{4-3} is hydrogen atom or C1-10 alkyl, R^{4-4} is C1-10 alkyl or

phenyl, D⁴⁻² is -CH₂ OH, -CH₂ OR⁴⁻⁵, hydroxy, -OR⁴⁻⁵, formyl, -CONR⁴⁻⁶R⁴⁻⁷, -CONR⁴⁻⁶SO₂R⁴⁻⁸, -CO-(NH-amino acid residue-CO)_m-OH, -O-(CO-amino acid residue-NH)_m-H, -COOR⁴⁻⁹, -OCO-R⁴⁻¹⁰, -COO-Z⁴⁻¹-Z⁴⁻²-Z⁴⁻³,



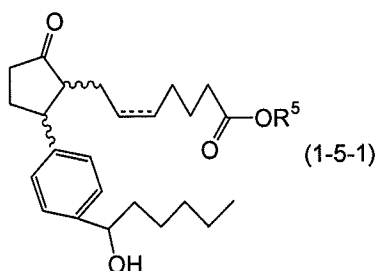
R⁴⁻⁶ and R⁴⁻⁷ are, each independently, hydrogen atom or C1-10 alkyl, R⁴⁻⁸ is C1-10 alkyl substituted by phenyl, R⁴⁻⁹ is C1-10 alkyl substituted by biphenyl optionally substituted by 1 to 3 substituents selected from C1-10 alkyl, C1-10 alkoxy and halogen atom or biphenyl substituted by 1 to 3 substituents selected from C1-10 alkyl, C1-10 alkoxy and halogen atom, R⁴⁻¹⁰ is phenyl or C1-10 alkyl, m is 1 or 2, Z⁴⁻¹ is C1-15 alkylene, C2-15 alkenylene or C2-15 alkynylene, Z⁴⁻² is -CO-, -OCO-, -COO-, -CONR^{4-Z1}-, -NR^{4-Z2}CO-, -O-, -S-, -SO₂-, -SO₂-NR⁴⁻-, -NR⁴SO₂-, -NR^{4-Z3}-, -NR^{4-Z4}CONR^{4-Z5}-, -NR^{4-Z6}COO-, -OCONR^{4-Z7}- or OCOO-, Z⁴⁻³ is hydrogen atom, C1-15 alkyl, C2-15 alkenyl, C2-15 alkynyl, ring Z⁴ or C1-10 alkoxy, C1-10 alkylthio, C1-10 alkyl-NR^{4-Z8}- or C1-10 alkyl substituted by ring Z⁴, ring Z⁴ is C3-15 mono-, bi- or tri-carbocyclic aryl which may be partially or fully saturated or 3 to 15 membered mono-, bi- or tri-heterocyclic aryl containing 1 to 4 hetero atoms selected from oxygen, nitrogen and sulfur atom which may be partially or fully saturated, R^{4-Z1}, R^{4-Z2}, R^{4-Z3}, R^{4-Z4}, R^{4-Z5}, R^{4-Z6}, R^{4-Z7} and R^{4-Z8} are, each independently, hydrogen atom or C1-15 alkyl, R^{4-Z1} and Z⁴⁻³ may be taken together with the nitrogen atom to which they are attached to form 5 to 7 membered saturated mono-heterocyclic ring, and the heterocyclic ring may contain other one hetero atom selected from oxygen, nitrogen and sulfur atom, ring Z⁴ and the saturated mono-heterocyclic ring formed by R^{4-Z1}, Z⁴⁻³ and the nitrogen atom to which they are attached may be substituted by 1-3 groups selected from C1-15

 R^{4-11} is C1-10 alkyl, C1-10 alkylthio, C1-10 alkyl substituted by ring 2 or

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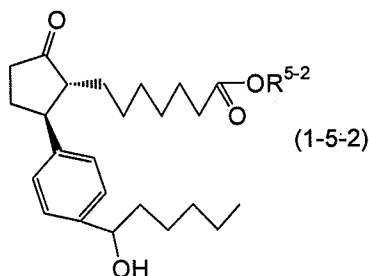
C1-10 alkoxy substituted by 1 to 4 halogen atoms, formyl, C1-10 alkyl substituted by hydroxy or C2-10 acyl, R^{15} , R^{16} and R^{17} are, each independently, (1) hydrogen atom or (2) C1-10 alkyl, R^{4-15} , R^{4-16} and R^{4-18} are, each independently, hydrogen atom or C1-10 alkyl, ring 5 may be substituted by 1 to 3 substituents selected from C1-10 alkyl, C2-10 alkenyl, C2-10 alkynyl, C1-10 alkoxy, C1-10 alkyl substituted by C1-10 alkoxy, halogen atom, hydroxy, C1-10 alkyl substituted by 1 to 3 halogen atom and C1-10 alkyl substituted by C1-10 alkoxy substituted by 1 to 3 halogen atoms, ring 1, ring 2, ring 3, ring 4 and ring 5 are, each independently, C3-15 mono-, bi- or tri-carbocyclic aryl which may be partially or fully saturated or 3 to 15 membered mono-, bi- or tri-heterocyclic aryl containing hetero atoms selected from 1 to 4 nitrogen, 1 to 2 oxygen and/or 1 to 2 sulfur atom which may be partially or fully saturated, with the proviso that, when E^4 is E^{4-2} , E^{4-2} is $U^{4-1}-U^{4-2}-U^{4-3}$, and U^{4-1} is C2 alkylene or C2 alkenylene, U^{4-2} is not -CHOH-; when U^{4-3} is C1-8 alkyl substituted by at least one hydroxy, $U^{4-1}-U^{4-2}$ is not C2 alkylene or C2 alkenylene; when A^4 is A^{4-1} and D^4 is D^{4-1} , E^4 is not E^{4-1} ; when T^4 is oxygen atom, X^4 is -CH₂-, D^4 is D^{4-1} , D^{4-1} is COOH, A^4 is A^{4-1} , A^{4-1} is C2-8 straight-chain alkylene, E^4 is E^{4-2} , E^{4-2} is $U^{4-1}-U^{4-2}-U^{4-3}$, U^{4-1} is C1-4 alkylene and U^{4-3} is C1-8 alkyl, U^{4-2} is not a bond, -CH₂-, -NR¹²- or carbonyl; when T^4 is oxygen atom, X^4 is -CH₂-, D^4 is D^{4-1} , D^{4-1} is COOH, A^4 is A^{4-2} , G^{4-1} is C1-4 alkylene, G^{4-2} is -O- or -NR⁴⁻¹-, G^{4-3} is a bond or C1-4 alkylene, E^4 is E^{4-2} , E^{4-2} is $U^{4-1}-U^{4-2}-U^{4-3}$, U^{4-1} is C1-4 alkylene and U^{4-3} is C1-8 alkyl, U^{4-2} is not a bond, -CH₂-, -NR⁴⁻¹²- or carbonyl; when T^4 is oxygen atom, X^4 is -CH₂-, D^4 is D^{4-1} , E is E^{4-2} , E^{4-2} is $U^{4-1}-U^{4-2}-U^{4-3}$, U^{4-1} is C2 alkylene or C2 alkenylene and U^{4-2} is -CO-, A^4 is not A^{4-1} or a salt thereof,

a compound represented by formula (1-5-1)



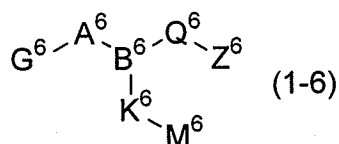
wherein R^5 is C1-20 saturated or unsaturated non-cyclic hydrocarbon or $-(CH_2)_{ma}R^{5-1}$, ma is 0 or an integer of 1-10, R^{5-1} is C3-7 cycloaliphatic ring or C4-10 aryl or heteroaryl ring (hetero atom is selected from the group consisting of N, O and S.) or salts thereof

a compound represented by formula (1-5-2)



wherein R^{5-2} is lower alkyl or salts thereof,

a compound represented by formula (1-6)



wherein A^6 is SO_2 or CO ; G^6 is Ar^6 , $Ar^{6-1}-V^6-Ar^{6-2}$, $Ar^6-(C1-6)$ alkylene, $Ar^6-CONH-(C1-6)$ alkylene, $R^{6-1}R^{6-2}$ -amino, oxy(C1-6) alkylene, amino substituted by Ar^6 or amino substituted by $Ar^6-(C1-4)$ alkylene and R^{6-11} , wherein R^{6-11} is hydrogen or C1-8 alkyl, R^{6-1} and R^{6-2} may be taken separately and are independently selected from hydrogen and C1-8 alkyl, or R^{6-1} and R^{6-2} are taken together with the nitrogen atom of the amino group to form a 5 or 6

membered azacycloalkyl, said azacycloalkyl optionally containing an oxygen atom and optionally mono-, di- or tri-substituted independently with up to two oxo, hydroxy, C1-4 alkyl, fluoro or chloro; B⁶ is nitrogen atom or CH;

Q⁶ is -(C2-6) alkylene-W⁶-(C1-3) alkylene-, said alkylenes each optionally substituted with up to four substituents independently selected from fluoro or C1-4 alkyl, -(C4-8) alkylene-, said alkylenes each optionally substituted with up to four substituents independently selected from fluoro or C1-4 alkyl, -X⁶-(C1-5) alkylene-, said alkylenes each optionally substituted with up to four substituents independently selected from fluoro or C1-4 alkyl, -(C1-5) alkylene-X⁶-, said alkylenes each optionally substituted with up to four substituents independently selected from fluoro or C1-4 alkyl, -(C1-3 alkylene)-X⁶-(C1-3) alkylene-, said alkylenes each optionally substituted with up to four substituents independently selected from fluoro or C1-4 alkyl, -(C1-4) alkylene-W⁶-X⁶-(C0-3) alkylene-, said alkylenes each optionally substituted with up to four substituents independently selected from fluoro or C1-4 alkyl, -(C0-4 alkylene)-X⁶-W⁶-(C1-3) alkylene-, said alkylenes each optionally substituted with up to four substituents independently selected from fluoro or C1-4 alkyl, -(C2-5 alkylene)-W⁶-X⁶-W⁶-(C1-3) alkylene-, wherein the two occurrences of W⁶ are independent of each other, said alkylenes each optionally substituted with up to four substituents each independently selected from fluoro or C1-4 alkyl, -(C1-4) alkylene-ethenylene-(C1-4) alkylene-, said alkylenes and said ethenylene each optionally substituted with up to four substituents each independently selected from fluoro or C1-4 alkyl, -(C1-4) alkylene-ethenylene-(C0-2) alkylene-X⁶-(C0-5) alkylene-, said alkylenes and said ethenylene each optionally substituted with up to four substituents each independently selected from fluoro or C1-4 alkyl, -(C1-4 alkylene)-ethenylene-(C0-2) alkylene-X⁶-W⁶-(C1-3) alkylene-, said alkylenes and said ethenylene each optionally substituted with up to four substituents each

independently selected from fluoro or C1-4 alkyl, -(C1-4) alkylene-ethynylene-(C1-4) alkylene-, said alkylenes and said ethynylene each optionally substituted with up to four substituents each independently selected from fluoro or C1-4 alkyl, or -(C1-4) alkylene-ethynylene- X^6 -(C0-3) alkylene-, said alkylenes and said ethynylene each optionally substituted with up to four substituents each independently selected from fluoro or C1-4 alkyl; Z^6 is carboxyl, C1-6 alkoxy, carbonyl, tetrazolyl, 1,2,4-oxadiazolyl, 5-oxo-1,2,4-oxadiazolyl, 5-oxo-1,2,4-thiadiazolyl, C1-4 alkylsulfonylcarbamoyl, or phenylsulfonylcarbamoyl; K^6 is a bond, C1-9 alkylene, thio(C1-4)alkylene, C1-4 alkylene-thio(C1-4) alkylene, C1-4 alkylene-oxy(C1-4)alkylene, or oxy(C1-4)alkylene, said C1-9 alkylene optionally mono-unsaturated and wherein, when K^6 is not a bond, K^6 is optionally mono-, di- or tri-substituted independently with chloro, fluoro, hydroxy or methyl; M^6 is $-Ar^{6-3}$, $-Ar^{6-4}-V1-Ar^{6-5}$, $-Ar^{6-4}-S-Ar^{6-5}$, $-Ar^{6-4}-SO-Ar^{6-5}$, $-Ar^{6-4}-SO_2-Ar^{6-5}$, or $-Ar^{6-4}-O-Ar^{6-5}$, Ar^6 is a partially saturated or fully unsaturated 5 to 8 membered ring optionally having 1 to 4 heteroatoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated 5 or 6 membered rings, taken independently, optionally having 1 to 4 heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated 5 or 6 membered rings, taken independently, optionally having 1 to 4 heteroatoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having 1 or 2 oxo groups substituted on carbon or 1 or 2 oxo groups substituted on sulfur; or Ar^6 is a fully saturated 5 to 7 membered ring having 1 or 2 heteroatoms selected independently from oxygen, sulfur and nitrogen;

Ar⁶⁻¹ and Ar⁶⁻² are each independently a partially saturated, fully saturated or fully unsaturated 5 to 8 membered ring optionally having 1 to 4 hetero atoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated 5 or 6 membered rings, taken independently, optionally having 1 to 4 heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated 5 or 6 membered rings, optionally having 1 to 4 hetero atoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having 1 or 2 oxo groups substituted on carbon or 1 or 2 oxo groups substituted on sulfur;

said Ar⁶, Ar⁶⁻¹ and Ar⁶⁻² moieties are optionally substituted on carbon or nitrogen, on one ring if the moiety is monocyclic, on one or both rings if the moiety is bicyclic, or on one, two or three rings if the moiety is tricyclic, with up to three substituents per moiety independently selected from R⁶⁻³, R⁶⁻⁴ and R⁶⁻⁵, wherein R⁶⁻³, R⁶⁻⁴ and R⁶⁻⁵ are independently hydroxy, nitro, halogen, carboxy, C1-7 alkoxy, (C1-4)alkoxy(C1-4)alkyl, C1-4 alkoxycarbonyl, C1-7 alkyl, C2-7 alkenyl, C2-7 alkynyl, C3-7 cycloalkyl, (C3-7)cycloalkyl(C1-4)alkyl, (C3-7)cycloalkyl(C1-4)alkanoyl, formyl, C1-8 alkanoyl, (C1-6)alkanoyl(C1-6)alkyl, C1-4 alkanoylamino, C1-4 alkoxycarbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C1-4)alkyl substituted aminocarbonylamino, sulfonamide, C1-4 alkylsulfonamide, amino, mono-N- or di-N,N-(C1-4) alkylamino, carbamoyl, mono-N- or di-N,N-(C1-4 alkyl)carbamoyl, cyano, thiol, C1-6 alkylthio, C1-6 alkylsulfinyl, C1-4 alkylsulfonyl, or mono-N- or di-N,N-(C1-4)alkylaminosulfinyl,

Ar⁶⁻³, Ar⁶⁻⁴ and Ar⁶⁻⁵ are each independently a partially saturated, fully saturated or fully unsaturated 5 to 8 membered ring optionally having 1 to 4 hetero atoms selected independently from oxygen, sulfur and nitrogen, or a bicyclic ring consisting of two fused independently partially saturated, fully saturated or fully unsaturated 5 or 6 membered rings, taken independently, optionally having 1 to 4 heteroatoms selected independently from nitrogen, sulfur and oxygen, or a tricyclic ring consisting of three fused independently partially saturated, fully saturated or fully unsaturated 5 or 6 membered rings, optionally having 1 to 4 hetero atoms selected independently from nitrogen, sulfur and oxygen, said partially or fully saturated ring, bicyclic ring or tricyclic ring optionally having 1 or 2 oxo groups substituted on carbon or 1 or 2 oxo groups substituted on sulfur;

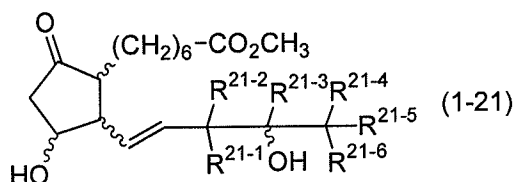
said Ar⁶⁻³, Ar⁶⁻⁴ and Ar⁶⁻⁵ moieties are optionally substituted on carbon or nitrogen, on one ring if the moiety is monocyclic, on one or both rings if the moiety is bicyclic, or on one, two or three rings if the moiety is tricyclic, with up to three substituents per moiety independently selected from R⁶⁻³¹, R⁶⁻⁴¹ and R⁶⁻⁵¹, wherein R⁶⁻³¹, R⁶⁻⁴¹ and R⁶⁻⁵¹ are independently hydroxy, nitro, halogen, carboxy, C1-7 alkoxy, C1-4 alkoxy(C1-4)alkyl, C1-4 alkoxy carbonyl, C1-7 alkyl, C2-7 alkenyl, C2-7 alkynyl, C3-7 cycloalkyl, (C3-7)cycloalkyl(C1-4)alkyl, (C3-7)cycloalkyl(C1-4)alkanoyl, formyl, C1-8 alkanoyl, (C1-6)alkanoyl(C1-6)alkyl, C1-4 alkanoylamino, C1-4 alkoxy carbonylamino, hydroxysulfonyl, aminocarbonylamino or mono-N-, di-N,N-, di-N,N'- or tri-N,N,N'-(C1-4)alkyl substituted aminocarbonyl, sulfonamide, C1-4 alkylsulfonamide, amino, mono-N- or di-N,N-(C1-4)alkylamino, carbamoyl, mono-N- or di-N,N-(C1-4)alkylcarbamoyl, cyano, thiol, C1-6 alkylthio, C1-6 alkylsulfinyl, C1-4 alkylsulfonyl or mono-N- or di-N,N-(C1-4)alkylaminosulfinyl, W⁶ is oxy, thio, sulfinio, sulfonyl, aminosulfonyl-, -mono-N-(C1-4)alkyleneaminosulfonyl-, sulfonylamino, N-(C1-

4)alkylenesulfonylamino, carboxamide, N-(C1-4)alkylenecarboxamide, carboxamideoxy, N-(C1-4)alkylenecarboxamideoxy, carbamoyl, -mono-N-(C1-4)alkylenecarbamoyl, carbamoyloxy or -mono-N-(C1-4)alkylenecarbamoyloxy, wherein said W^6 alkyl groups are optionally substituted on carbon with 1 to 3 fluorines;

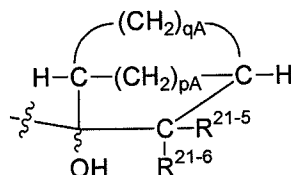
X^6 is a 5 or 6 membered aromatic ring optionally having 1 or 2 heteroatoms selected independently from oxygen, nitrogen, and sulfur; said ring optionally mono-, di- or tri-substituted independently with halo, (C1-3) alkyl, trifluoromethyl, trifluoromethyloxy, difluoromethyloxy, hydroxyl, (C1-4) alkoxy, or carbamoyl;

R^{6-1} , R^{6-2} , R^{6-3} , R^{6-4} , R^{6-5} , R^{6-11} , R^{6-31} , R^{6-41} and R^{6-51} , when containing an alkyl, alkylene, alkenylene or alkynylene moiety, are optionally mono-, di- or tri-substituted on carbon independently with halo or hydroxy; and V and V1 are each independently a bond, thio(C1-4)alkylene, C1-4 alkylthio, C1-4 alkyleneoxy, oxy(C1-4)alkylene or C1-3 alkylene optionally mono- or di-substituted independently with hydroxy or fluoro; with the provisos that: (a) when K^6 is C2-4 alkylene and M^6 is Ar^{6-3} and Ar^{6-3} is cyclopent-1-yl, cyclohex-1-yl, cyclohept-1-yl or cyclooct-1-yl then said C5-8 cycloalkyl substituents are not substituted at the one position with hydroxy; and (b) when K^6 is a bond; G^6 is phenyl, phenylmethyl, substituted phenyl or substituted phenylmethyl; Q^6 is C3-8 alkylene; and M^6 is Ar^{6-3} or $Ar^{6-4}-Ar^{6-5}$, then A is sulfonyl or a salt thereof,

a compound represented by formula (1-21)

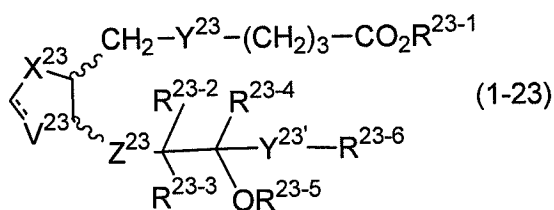


wherein R^{21-1} and R^{21-2} is hydrogen, R^{21-3} is selected from the group consisting of hydrogen, or together with R^{21-4} is a C4 methylene such that a cycloalkyl of up to 6 carbon atoms inclusive is formed, or together with R^{21-4} is a bicycloalkyl or bicycloalkenyl moiety having the formula



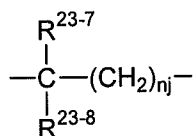
wherein p_A is 0 or 1, q_A is 2 or 3, and wherein the double bond of such bicycloalkenyl is in the q_A bridge.); R^{21-4} is together with R^{21-3} forms a cycloalkyl or bicycloalkyl or bicycloalkenyl as defined above, or together with R^{21-5} is a methylene chain of 3 carbon atoms such that a cycloalkyl of 4 carbon atoms inclusive is formed; R^{21-5} is selected from the group consisting of hydrogen or together with R^{21-4} forms a cycloalkyl as defined above; and R^{21-6} is selected from the group consisting of hydrogen or straight-chain alkyl having 8 carbon atoms or salts thereof, and

a compound represented by formula (1-23)



wherein R^{23-1} , R^{23-2} and R^{23-3} is hydrogen or C1-7 alkyl; R^{23-4} is C1-7 alkyl; R^{23-5} is hydrogen, C1-7 alkyl or C1-7 alkanoyl; R^{23-6} is C2-4 alkyl or C5-7 cycloalkyl; X^{23} is carbonyl, hydroxymethylene or alkanoyloxymethylene, (with proviso that alkanoyl includes 1 to 7 carbon atoms.); V^{23} is methylene, hydroxymethylene or alkanoyloxymethylene, (with proviso that

alkanoyl includes 1 to 7 carbon atoms.); Y^{23} is ethylene or vinylene, $Y^{23'}$ is vinylene, ethynylene or the following group



wherein n_j is 0 or 1, Y^{23-7} and Y^{23-8} are hydrogen or C1-7 alkyl.), Z^{23} is ethylene, vinylene or ethynylene or salts thereof.

28. (Previously presented) The method according to claim 27, wherein the compound is one or more compounds selected from

- (1) (5Z,9 β ,11 α ,13E)-17,17-propano-11,16-dihydroxy-9-chloro-20-norprosta-5,13-dienoic acid,
- (2) (5Z,9 β ,11 α ,13E)-17,17-propano-11,16-dihydroxy-9-chloroprosta-5,13,19-trienoic acid,
- (3) trans-2-(4-(1-hydroxyhexyl)phenyl)-5-oxocyclopentaneheptanoic acid,
- (4) 2-[3-(4-tert-butylbenzyl)-N-(pyridin-3-ylsulfonyl)amino-methyl]phenoxy]acetic acid,
- (5) [1R[1 α ,2 β (1E,4R*),3 α]]-3-hydroxy-2-[4-hydroxy-4-(1-propylcyclobutyl)-1-butenyl]-5-oxocyclopentane-heptanoic acid methyl ester,
- (6) (2R,3R,4R)-4-hydroxy-2-(7-hydroxyheptyl)-3-[(E)-(4RS)-(4-hydroxy-4-methyl-1-octenyl)]cyclopentanone, and
- (7) (+/-)-15-deoxy-16- α,β -hydroxy-16-methyl PGE1 methylester.

29. (Withdrawn) The method according to claim 11, wherein the substance having an EP3 agonist activity is one or more compounds selected from a compound described in WO98/34916, a compound described in JP-A-8-239356, a compound described in US4,692,464, a compound described in JP-A-61-249951, a compound described in US4,863,961 and a compound described in US3,985,791.

30. (withdrawn) The method according to claim 29, wherein the compound is one or more compounds selected from

- (1) 11 α ,15 α -dimethoxy-9-oxoprost-5Z,13E-dienoic acid,
- (2) 2-[5-[2-[N-(diphenylmethyl)carbamoyl]ethyl]naphthalen-1-yloxy]acetic acid,
- (3) (1S,5S,6R,7R)-5-[7-hydroxy-6-[3(S)-hydroxy-3-methyl-1(E)-octenyl]bicyclo[3.3.0]oct-2-ene-3-yl]pentanoic acid,
- (4) (-)-[1(R)-[1 α (Z),2 β (R*),3 α]]-7-[3-hydroxy-2-(2-hydroxy-3-phenylpropoxy)-5-oxocyclopentyl]-4-heptenoic acid 4-(benzoylamino)phenylester,
- (5) methyl-7-(2 β -(6-(1-cyclopentyl-yl)-4R-hydroxy-4-methyl-1E,5E-hexadienyl)-3 α -hydroxy-5-oxo-1R,1 α -cyclopentyl)-4Z-heptenoic acid, and
- (6) 9-oxo-11 α ,15 α -dihydroxy-16-phenoxy-17,18,19,20-tetranorprosta-4,5,13-trans-trienoic acid methyl ester.

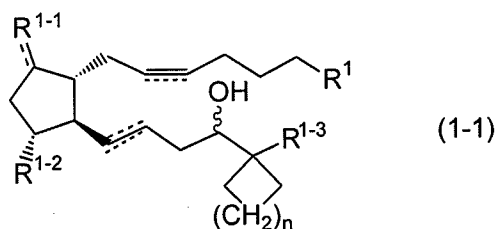
31. (withdrawn) The method according to claim 11, wherein the compound having an EP3 agonist activity is 16-phenoxy- ω -17,18,19,20-tetranor-PGE₂ methylsulfonamide or a salt thereof.

32. (withdrawn) An agent for treating cartilage-related disease comprising a combination of one or more substances selected from transforming growth factor- β , insulin-like growth factor, basic fibroblast growth factor, epidermal growth factor, growth hormone and platelet-derived growth factor, and a substance having an EP2 and/or EP3 agonist activity.

33. (withdrawn) A method for producing a cartilage graft, which comprises using a substance having an EP2 and/or EP3 agonist activity.

34. (withdrawn) A method for screening an agent for treating cartilage-related disease comprising a substance having an EP2 and/or EP3 agonist activity, which comprises correlating the EP2 and/or EP3 agonist activity.

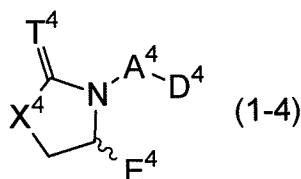
35. (currently amended) A method for treating cartilage-related disease, which ~~comprises~~ consists of administering a composition ~~consisting essentially of~~ consisting of a substance, as an active ingredient, having an EP2 agonist activity selected from a compound represented by formula (1-1)



wherein R¹ is carboxy or hydroxymethyl, R¹⁻¹ is oxo, methylene or halogen atom, R¹⁻² is hydrogen atom, hydroxy or C1-4 alkoxy, R¹⁻³ is hydrogen atom, C1-8 alkyl, C2-8 alkenyl, C2-8

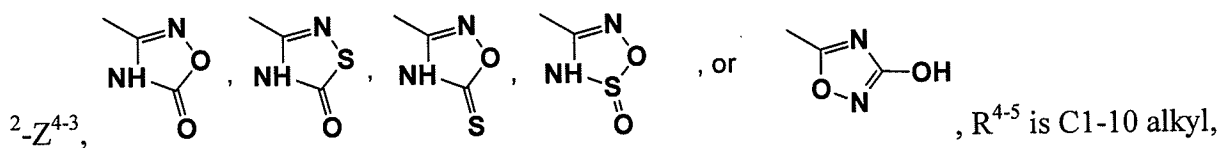
alkynyl, or C1-8 alkyl, C2-8 alkenyl or C2-8 alkynyl substituted by 1-3 substituents selected from the following (1) to (5): (1) halogen atom, (2) C1-4 alkoxy, (3) C3-7 cycloalkyl, (4) phenyl or (5) phenyl substituted by 1-3 substituents selected from halogen atom, C1-4 alkyl, C1-4 alkoxy, nitro or trifluoromethyl; n is 0 or 1-4; with the proviso that (1) when 5-6 position is triple bond, 13-14 position is not triple bond, (2) when 13-14 position is double bond, the double bond represents E form, Z form or mixture of EZ form

or a salt thereof, and a compound represented by formula (1-4)



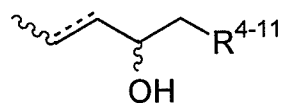
wherein T^4 is oxygen atom or sulfur atom, X^4 is $-CH_2-$, $-O-$ or $-S-$, A^4 is A^{4-1} or A^{4-2} , A^{4-1} is C2-8 straight-chain alkylene optionally substituted by 1 to 2 C1-4 alkyl, C2-8 straight-chain alkenylene optionally substituted by 1 to 2 C1-4 alkyl or (3) C2-8 straight-chain alkynylene optionally substituted by 1 to 2 C1-4 alkyl, A^{4-2} is $-G^{4-1}-G^{4-2}-G^{4-3}-$, G^{4-1} is C1-4 straight-chain alkylene optionally substituted by 1 to 2 C1-4 alkyl, C2-4 straight-chain alkenylene optionally substituted by 1 to 2 C1-4 alkyl or C2-4 straight-chain alkynylene optionally substituted by 1 to 2 C1-4 alkyl, G^{4-2} is $-Y^4-$, $-ring\ 1-$, $-Y^4-ring\ 1-$, $-ring\ 1-Y^4-$ or $-Y^4-C1-4\ alkylene-ring\ 1-$, Y^4 is $-S-$, $-SO-$, $-SO_2-$, $-O-$ or $-NR^{4-1}-$, R^{4-1} is hydrogen atom, C1-10 alkyl or C2-10 acyl, G^{4-3} is a bond, C1-4 straight-chain alkylene optionally substituted by 1 to 2 C1-4 alkyl, C2-4 straight-chain alkenylene optionally substituted by 1 to 2 C1-4 alkyl or C2-4 straight-chain alkynylene optionally substituted by 1 to 2 C1-4 alkyl, D^4 is D^{4-1} or D^{4-2} , D^{4-1} is $-COOH$, $-COOR^{4-2}$, tetrazol-5-yl or $-CONR^{4-3}SO_2R^{4-4}$, R^{4-2} is C1-10 alkyl, phenyl, C1-10 alkyl substituted by phenyl or biphenyl, R^{4-3} is hydrogen atom or C1-10 alkyl, R^{4-4} is C1-10 alkyl or phenyl, D^{4-2} is $-CH_2OH$, -

$\text{CH}_2\text{OR}^{4-5}$, hydroxy, $-\text{OR}^{4-5}$, formyl, $-\text{CONR}^{4-6}\text{R}^{4-7}$, $-\text{CONR}^{4-6}\text{SO}_2\text{R}^{4-8}$, $-\text{CO}-(\text{NH-amino acid residue-CO})_m-\text{OH}$, $-\text{O}-(\text{CO-amino acid residue-NH})_m-\text{H}$, $-\text{COOR}^{4-9}$, $-\text{OCO-R}^{4-10}$, $-\text{COO-Z}^{4-1}-\text{Z}^{4-2}$



R^{4-6} and R^{4-7} are, each independently, hydrogen atom or C1-10 alkyl, R^{4-8} is C1-10 alkyl substituted by phenyl, R^{4-9} is C1-10 alkyl substituted by biphenyl optionally substituted by 1 to 3 substituents selected from C1-10 alkyl, C1-10 alkoxy and halogen atom or biphenyl substituted by 1 to 3 substituents selected from C1-10 alkyl, C1-10 alkoxy and halogen atom, R^{4-10} is phenyl or C1-10 alkyl, m is 1 or 2, Z^{4-1} is C1-15 alkylene, C2-15 alkenylene or C2-15 alkynylene, Z^{4-2} is $-\text{CO}-$, $-\text{OCO}-$, $-\text{COO}-$, $-\text{CONR}^{4-\text{Z}1}-$, $-\text{NR}^{4-\text{Z}2}\text{CO}-$, $-\text{O}-$, $-\text{S}-$, $-\text{SO}_2-$, $-\text{SO}_2-\text{NR}^{4-}$, $-\text{NR}^{4-\text{Z}3}\text{SO}_2-$, $-\text{NR}^{4-\text{Z}4}\text{CONR}^{4-\text{Z}5}-$, $-\text{NR}^{4-\text{Z}6}\text{COO}-$, $-\text{OCONR}^{4-\text{Z}7}-$ or $\text{OCOO}-$, Z^{4-3} is hydrogen atom, C1-15 alkyl, C2-15 alkenyl, C2-15 alkynyl, ring Z^4 or C1-10 alkoxy, C1-10 alkylthio, C1-10 alkyl- $\text{NR}^{4-\text{Z}8}-$ or C1-10 alkyl substituted by ring Z^4 , ring Z^4 is C3-15 mono-, bi- or tri-carbocyclic aryl which may be partially or fully saturated or 3 to 15 membered mono-, bi- or tri-heterocyclic aryl containing 1 to 4 hetero atoms selected from oxygen, nitrogen and sulfur atom which may be partially or fully saturated, $\text{R}^{4-\text{Z}1}$, $\text{R}^{4-\text{Z}2}$, $\text{R}^{4-\text{Z}3}$, $\text{R}^{4-\text{Z}4}$, $\text{R}^{4-\text{Z}5}$, $\text{R}^{4-\text{Z}6}$, $\text{R}^{4-\text{Z}7}$ and $\text{R}^{4-\text{Z}8}$ are, each independently, hydrogen atom or C1-15 alkyl, $\text{R}^{4-\text{Z}1}$ and Z^{4-3} may be taken together with the nitrogen atom to which they are attached to form 5 to 7 membered saturated mono-heterocyclic ring, and the heterocyclic ring may contain other one hetero atom selected from oxygen, nitrogen and sulfur atom, ring Z^4 and the saturated mono-heterocyclic ring formed by $\text{R}^{4-\text{Z}1}$, Z^{4-3} and the nitrogen atom to which they are attached may be substituted by 1-3 groups selected from C1-15 alkyl, C2-15 alkenyl, C2-15 alkynyl, C1-10 alkyl substituted by C1-10 alkoxy, C1-10 alkylthio and C1-10

alkyl-NR^{4-Z9}-; R^{4-Z9} is hydrogen atom or C1-10 alkyl, E⁴ is E⁴⁻¹ or E⁴⁻², E⁴⁻¹ is



, R⁴⁻¹¹ is C1-10 alkyl, C1-10 alkylthio, C1-10 alkyl substituted by ring 2 or C1-10 alkyl substituted by -W⁴⁻¹-W⁴⁻²- ring 2, W⁴⁻¹ is -O-, -S-, -SO-, -SO₂-, -NR⁴⁻¹¹⁻¹-, carbonyl, -NR⁴⁻¹¹⁻¹SO₂-, carbonylamino or aminocarbonyl, R⁴⁻¹¹⁻¹ is hydrogen atom, C1-10 alkyl or C2-10 acyl, W⁴⁻² is C1-8 alkyl optionally substituted by C1-4 alkyl, halogen or hydroxy, E⁴⁻² is U⁴⁻¹-U⁴⁻²-U⁴⁻³ or ring 4, U⁴⁻¹ is C1-4 alkylene, C2-4 alkenylene, C2-4 alkynylene, -ring 3-, C1-4 alkylene-ring 3-, C2-4 alkenylene-ring 3-or C2-4 alkynylene-ring 3-, U⁴⁻² is a bond, -CH₂-, -CHOH-, -O-, -S-, -SO-, -SO₂-, -NR⁴⁻¹²-, carbonyl, -NR⁴⁻¹²SO₂-, carbonylamino or aminocarbonyl, R⁴⁻¹² is hydrogen atom, C1-10 alkyl or C2-10 acyl, U⁴⁻³ is C1-8 alkyl optionally substituted by 1 to 3 substituents selected from C1-10 alkyl, halogen, hydroxy, alkoxy, alkylthio and -NR⁴⁻¹³R⁴⁻¹⁴, C1-8 alkenyl optionally substituted by 1 to 3 substituents selected from C1-10 alkyl, halogen, hydroxy, alkoxy, alkylthio and -NR⁴⁻¹³R⁴⁻¹⁴, C1-8 alkynyl optionally substituted by 1 to 3 substituents selected from C1-10 alkyl, halogen, hydroxy, alkoxy, alkylthio and -NR⁴⁻¹³R⁴⁻¹⁴, C1-8 alkyl substituted by ring 4 or ring 4, R⁴⁻¹³ and R⁴⁻¹⁴ are, each independently, halogen atom or C1-10 alkyl, ring 1, ring 2, ring 3 and ring 4 may be substituted by 1 to 5 substituents selected from C1-10 alkyl, C2-10 alkenyl, C2-10 alkynyl, C1-10 alkoxy, C1-10 alkylthio, halogen atom, hydroxy, nitro, -NR⁴⁻¹⁵R⁴⁻¹⁶, C1-10 alkyl substituted by C1-10 alkoxy, C1-10 alkyl substituted by 1 to 3 halogen atoms, C1-10 alkyl substituted by C1-10 alkoxy substituted by 1 to 3 halogen atoms, C1-10 alkyl substituted by -NR⁴⁻¹⁵R⁴⁻¹⁶, ring 5, -O-ring 5, C1-10 alkyl substituted by ring 5, C2-10 alkenyl substituted by ring 5, C2-10 alkynyl substituted by ring 5, C1-10 alkoxy substituted by ring 5, C1-10 alkyl substituted by -O-ring 5, COOR⁴⁻¹⁷, C1-10 alkoxy substituted by 1 to 4 halogen atoms, formyl, C1-10 alkyl substituted by hydroxy or

C2-10 acyl, R^{15} , R^{16} and R^{17} are, each independently, (1) hydrogen atom or (2) C1-10 alkyl, R^{4-15} , R^{4-16} and R^{4-18} are, each independently, hydrogen atom or C1-10 alkyl, ring 5 may be substituted by 1 to 3 substituents selected from C1-10 alkyl, C2-10 alkenyl, C2-10 alkynyl, C1-10 alkoxy, C1-10 alkyl substituted by C1-10 alkoxy, halogen atom, hydroxy, C1-10 alkyl substituted by 1 to 3 halogen atom and C1-10 alkyl substituted by C1-10 alkoxy substituted by 1 to 3 halogen atoms, ring 1, ring 2, ring 3, ring 4 and ring 5 are, each independently, C3-15 mono-, bi- or tri-carbocyclic aryl which may be partially or fully saturated or 3 to 15 membered mono-, bi- or tri-heterocyclic aryl containing hetero atoms selected from 1 to 4 nitrogen, 1 to 2 oxygen and/or 1 to 2 sulfur atom which may be partially or fully saturated. With the proviso that, when E^4 is E^{4-2} , E^{4-2} is $U^{4-1}-U^{4-2}-U^{4-3}$, and U^{4-1} is C2 alkylene or C2 alkenylene, U^{4-2} is not -CHOH-; when U^{4-3} is C1-8 alkyl substituted by at least one hydroxy, $U^{4-1}-U^{4-2}$ is not C2 alkylene or C2 alkenylene; when A^4 is A^{4-1} and D^4 is D^{4-1} , E^4 is not E^{4-1} ; when T^4 is oxygen atom, X^4 is -CH₂-, D^4 is D^{4-1} , D^{4-1} is COOH, A^4 is A^{4-1} , A^{4-1} is C2-8 straight-chain alkylene, E^4 is E^{4-2} , E^{4-2} is $U^{4-1}-U^{4-2}-U^{4-3}$, U^{4-1} is C1-4 alkylene and U^{4-3} is C1-8 alkyl, U^{4-2} is not a bond, -CH₂-, -NR¹²- or carbonyl; when T^4 is oxygen atom, X^4 is -CH₂-, D^4 is D^{4-1} , D^{4-1} is COOH, A^4 is A^{4-2} , G^{4-1} is C1-4 alkylene, G^{4-2} is -O- or -NR⁴⁻¹-, G^{4-3} is a bond or C1-4 alkylene, E^4 is E^{4-2} , E^{4-2} is $U^{4-1}-U^{4-2}-U^{4-3}$, U^{4-1} is C1-4 alkylene and U^{4-3} is C1-8 alkyl, U^{4-2} is not a bond, -CH₂-, -NR⁴⁻¹²- or carbonyl; when T^4 is oxygen atom, X^4 is -CH₂-, D^4 is D^{4-1} , E is E^{4-2} , E^{4-2} is $U^{4-1}-U^{4-2}-U^{4-3}$, U^{4-1} is C2 alkylene or C2 alkenylene and U^{4-2} is -CO-, A^4 is not A^{4-1} ,

or a salt thereof, and a pharmaceutically acceptable carrier,

to a subject in need of stimulating chondrocyte growth.

36. (previously presented) The method according to claim 35, wherein the substance having an EP2 agonist activity is one or more compounds selected from

(1) (5Z,9 β ,11 α ,13E)-17,17-propano-11,16-dihydroxy-9-chloro-20-norprosta-5,13-dienoic acid and

(2) (5Z,9 β ,11 α ,13E)-17,17-propano-11,16-dihydroxy-9-chloroprosta-5,13,19-trienoic acid,

or a salt thereof.